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ORIGINAL ARTICLE

Clinical characteristics and psychosocial impact of different reflux time in gastroesophageal reflux disease patients

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Background/purpose: Gastroesophageal reflux disease (GERD) is an emerging disease, and can impair quality of life and sleep. This study aimed to investigate whether GERD patients with different timings of reflux symptoms have different clinical characteristics.
Methods: This study prospectively enrolled individuals who underwent upper gastrointestinal endoscopy during a health checkup. Each participant completed all questionnaires including Reflux Disease Questionnaire, Nighttime GERD questionnaire, Pittsburg Sleep Quality Index, Taiwanese Depression Questionnaire, and State-Trait Anxiety Inventory. Combined reflux was defined as the timing of reflux symptoms occurring at both daytime and nighttime.
Results: A total of 2604 participants were enrolled. Of them, 651 symptomatic GERD patients, according to the Reflux Disease Questionnaire score, were recruited for final analysis. Of them, 224 (34.4%) had erosive esophagitis on endoscopy. According to the timing of reflux symptoms, 184 (28.3%) were assigned to the daytime reflux group, 71 (10.9%) to the nighttime reflux group, and 396 (60.8%) to the combined reflux group. In *post hoc* analysis, the combined reflux group had a significantly higher Reflux Disease Questionnaire score than the daytime reflux group ($p < 0.0001$). Combined and nighttime reflux groups had higher body mass index and longer duration (> 12 years) of education than the daytime reflux group ($p < 0.05$). There was no difference in Pittsburg Sleep Quality Index, Taiwanese Depression Questionnaire, and State-Trait Anxiety Inventory scores among three groups.

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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Conclusion: GERD patients with combined daytime and nighttime reflux of have more troublesome symptoms than those with daytime reflux. GERD patients with different timings of reflux symptoms have different clinical characteristics in terms of body mass index and duration of education, but not in terms of esophageal inflammation, quality of sleep, and psychosocial status.

Introduction

Gastroesophageal reflux disease (GERD) is the most common gastrointestinal diagnosis in outpatient clinics, incurring high expenses across the world.[1] The incidence increases fivefold in most Western countries and appears to be rising in some developed Asian countries.[2] It can reduce the quality of life and complicate life with esophagitis, bleeding, stricture, or even esophageal adenocarcinoma.[3] In clinical practice, the diagnosis depends on the typical reflux symptoms, including heartburn and/or acid regurgitation. However, not all the patients with typical reflux symptoms have the evidence of mucosal injury on endoscopy.[4] Patients with GERD can be categorized according to the timing of reflux symptoms they predominantly experience. Several recent studies have demonstrated that nighttime symptoms are not unusual, affecting between 72% and 79% of GERD patients.[5–7] Frequent nighttime heartburn has been reported to impair health-related quality of life and work productivity of GERD patients compared with minimal or no nighttime symptoms.[8] In addition, recent studies have also demonstrated poor quality of sleep and sleep disturbances among patients with nighttime GERD.[9–11]

There is scanty information about clinical characteristics in GERD patients with nighttime symptoms versus those with other timings of reflux symptoms. Furthermore, there are no data on the impact of nighttime reflux on the status of mood such as anxiety and depression. Thus, our study aimed to examine, using a large-scale health examination cohort, whether GERD patients, categorized based on the timing of reflux symptoms, have different characteristics and psychological comorbidities.

Methods

Study participants

A total of 2752 participants who came to the Health Examination Centers of Taipei, Tiawan and Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan for medical check-up from March 2012 to August 2013 were recruited in the study. Individuals aged younger than 20 years or older than 70 years and with insufficient answers to the questionnaires ($n = 163$) were excluded. Of them, 651 who were diagnosed to have symptomatic GERD according to the Reflux Disease Questionnaire (RDQ) score were recruited for the final analysis. The RDQ was an instrument used for the diagnosis of symptomatic GERD and previously validated in Chinese populations.[12–14] The time of reflux symptoms including heartburn and/or acid regurgitation within the previous 3 months was determined using nighttime gastroesophageal reflux disease (NTG) questionnaire. According to the NTG questionnaire, these individuals were divided into three groups: "daytime group" including adults who experience only daytime symptoms, "nighttime group" including adults who experience only nighttime symptoms, and "combined group" defined as adults who experience both daytime and nighttime symptoms. Nighttime symptoms were defined as reflux symptoms occurring at the time of going to bed, in sleep, or just after waking up. The daytime group included adults with reflux symptoms at least 1 day per week but without nighttime symptoms, and the nighttime group included adults with reflux symptoms at least 1 night per week but without daytime symptoms. The combined group consisted of adults with both daytime and nighttime reflux symptoms at least once per week. The ethics committees of Taipei and Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation approved this study, and each participant provided informed consent.

Questionnaires

In this study, a face-to-face interview was conducted using a questionnaire during the health examination visit. The questionnaires included RDQ, NTG questionnaire, Pittsburg Sleep Quality Index (PSQI), Taiwanese Depression Questionnaire (TDQ), and State-Trait Anxiety Inventory (STAI). The RDQ was an instrument used for the diagnosis of symptomatic GERD. It examined symptoms of heartburn, acid regurgitation, and dyspepsia, and included 12 questions regarding the frequency and severity of burning and pain behind the breastbone, acidic taste in the mouth, movement of materials upward from the stomach, and burning and pain in the upper stomach.[15,16] The response option was scaled from 0 to 5 points. After excluding the dyspepsia scale, scores of RDQ ranged from 0 to 40. The PSQI was an effective instrument for measuring the quality and patterns of sleep by examining seven domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction over the past month. Scoring of answers ranges from 0 to 3, with a sum score of $\geq$ 5 indicating a "poor" sleeper.[17] The TDQ has 18 items with a 4-point scale. It is a culturally specific depression instrument, effective for screening of depression in Taiwanese people and has satisfactory reliability and validity.[18] The participants were guided to rate each item on a scale from 0 to 3 on the basis of "how often you felt the physical and emotional aspects during the past week." TDQ scores range from 0 to 54. The STAI is a commonly used measurement of trait and state anxiety.[19] It can be used in clinical settings

to diagnose anxiety and distinguish it from depressive syndromes. It has 20 items for assessing trait anxiety, along with 20 items for state anxiety. All items are rated on a 4-point scale (e.g., from "almost never" to "almost always"); hence, higher scores indicate greater anxiety.

Demographic and medical information

Demographic data were collected, including gender, age, body mass index (BMI), education, family income, and history of diabetes mellitus, hypertension, and hyperlipidemia. Furthermore, medical information related to GERD was included. Esophagogastroduodenoscopy was performed on each participant. Standardized sedated endoscopic examination of the esophagus, stomach, and duodenum was performed, and erosive esophagitis was graded from A to D according to the Los Angeles classification.[20] Experienced endoscopists, who were blinded to the results of the questionnaires, performed all the procedures. Any discordance in the diagnosis needed discussion, and the final diagnosis was made by consensus of three experienced endoscopists. An autoanalyzer measured serum fasting blood glucose, triglyceride, total cholesterol, low-density lipoprotein, and high-density lipoprotein (Roche analytics; Roche Professional Diagnostics, Penzberg, Germany). Metabolic syndrome was determined based on the National Cholesterol Education Program Adult Treatment Panel III as the presence of at least three of the following five characteristics: the presence of abdominal obesity (a waist circumference of $\geq$ 90 cm for Taiwanese men and $\geq$ 80 cm for Taiwanese women), triglyceride concentration $\geq$ 150 mg/dL, high-density lipoprotein cholesterol concentration $<$ 40 mg/dL in men and $<$ 50 mg/dL in women, systolic blood pressure $\geq$ 130 mmHg or diastolic blood pressure $\geq$ 85 mmHg; or fasting plasma glucose $\geq$ 100 mg/dL.[21]

Statistical analysis

Categorical data were presented as percentages, while continuous data were presented as the mean with standard deviations. Chi-square test and analysis of variance followed by Turkey's *post hoc* test were used to analyze categorical and continuous variables, respectively. The association between NTG status and potential risk factors was measured by odds ratio. The nighttime and mixed groups were compared with the daytime group (i.e., the reference group). Adjusted odds ratios and 95% confidence intervals as well as p values were estimated based on stepwise multiple logistic regression. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA). All tests were two sided, and $p < 0.05$ was considered statistically significant.

Results

Demographic and clinical characteristics of GERD patients with different timings of reflux symptoms

A total of 651 GERD patients were recruited for the final analysis. Of them, 224 (34.4%) had erosive esophagitis on

Table 1 Demographic data and questionnaire scores among three different time groups of GERD patients.

Time of reflux symptoms	Daytime (n = 184)	Nighttime (n = 71)	Combined (n = 396)	p
Male	94 (51.1)	47 (66.2)	226 (57.1)	0.08
Age (y)	51.35 ± 9.74	49.73 ± 11.09	49.61 ± 9.69	0.13
BMI (kg/m^2)	23.67 ± 3.36	25.09 ± 4.04	24.68 ± 3.79	0.003 [a,b]
WHR	0.88 ± 0.08	0.90 ± 0.08	0.88 ± 0.08	0.55
Duration of education (y)				0.02
<9	42 (22.8)	11 (15.5)	59 (14.9)	
9–12	62 (33.7)	16 (22.5)	139 (35.1)	
>12	80 (43.5)	44 (62)	198 (50)	
Income				0.5
Enough	106 (57.6)	35 (49.3)	210 (53)	
Rich	70 (38)	33 (46.5)	159 (40.2)	
Poor	8 (4.4)	3 (4.2)	27 (6.8)	
Clinic for GERD	94 (51.1)	28 (39.4)	239 (60.4)	0.002
Questionnaire				
RDQ score	5.14 ± 5.13	5.37 ± 5.47	8.75 ± 6.87	<0.0001 [b,c]
PSQI score	6.49 ± 2.10	6.48 ± 2.06	6.81 ± 2.37	0.22
PSQI ≥5	33 (17.9)	14 (19.7)	62 (15.7)	0.61
Depression: TDQ score	26.68 ± 7.18	27.68 ± 7.83	29.65 ± 9.6	0.001 [b]
Anxiety: STAI score	42.65 ± 6.12	42.92 ± 7.38	42.83 ± 6.18	0.93

BMI = body mass index GERD = gastroesophageal reflux disease;; PSQI = Pittsburg Sleep Quality Index; RDQ = reflux disease questionnaire; STAI = State-Trait Anxiety Inventory; TDQ = Taiwanese Depression Questionnaire; WHR = waist–hip ratio.
Data are presented as n (%) or mean (standard deviation).
[a] Between daytime and nighttime.
[b] Between daytime and combined.
[c] Between nighttime and combined.

Table 2 Comparison of clinical data among three different time groups of GERD patients.

Factors	Daytime (n = 184)	Nighttime (n = 71)	Combined (n = 396)	p
Erosive esophagitis	61 (33.2)	24 (33.8)	139 (35.1)	0.89
Hiatus hernia	9 (5)	5 (7)	15 (4.1)	0.54
Helicobacter pylori	47 (25.8)	18 (25.4)	80 (20.5)	0.31
Hypertension	27 (15.8)	10 (14.7)	70 (18.6)	0.59
Diabetes mellitus	10 (5.9)	5 (7.4)	31 (8.2)	0.61
Hyperlipidemia	24 (14)	11 (16.2)	48 (12.8)	0.73
Metabolic syndrome	46 (25)	22 (31)	131 (33.1)	0.14
Waist (cm)	84.04 ± 10.25	87.17 ± 11.52	85.51 ± 10.63	0.09
Systolic blood pressure (mmHg)	118.79 ± 16.06	117.12 ± 14.13	120.32 ± 15.54	0.23
Diastolic blood pressure (mmHg)	73.92 ± 12.79	74.64 ± 11.80	74.90 ± 12.10	0.69
Glucose (mg/dL)	95.49 ± 18.72	98.31 ± 19.07	99.20 ± 24.75	0.19
Cholesterol (mg/dL)	196.68 ± 40.10	195.97 ± 41.17	193.05 ± 36.82	0.54
Triglyceride (mg/dL)	115.29 ± 68.75	139.01 ± 102.46	130.35 ± 83.74	0.05
HDL (mg/dL)	52.07 ± 14.01	48.03 ± 14.64	48.53 ± 13.90	0.01[a]

GERD = gastroesophageal reflux disease; HDL = high-density lipoprotein.
Data are presented as n (%) or mean (standard deviation).
[a] Between daytime and combined.

endoscopy. According to the timing of reflux symptoms, 184 (28.3%) were in the daytime group, 71 (10.9%) in the nighttime group, and 396 (60.8%) in the combined group. The demographic and clinical data are shown in Tables 1 and 2. The combined group had a higher RDQ score than the daytime or nighttime group ($p < 0.0001$). The combined group had a significantly higher TDQ score than the daytime group ($p = 0.0006$). Among the three groups, there was a significant difference in BMI, duration of education, and clinic for GERD and serum high-density lipoprotein levels. However, age, sex, income, diabetes mellitus, hypertension, hyperlipidemia, metabolic syndrome, serum glucose, triglyceride, cholesterol, waist circumference, blood pressure, and PSQI and STAI scores were comparable among the three groups. There was also no significant difference in the presence of erosive esophagitis, hiatus hernia, or *Helicobacter pylori* infection among the three groups.

Clinical factors in patients with nighttime or combined reflux symptoms compared with those with daytime reflux symptoms, using multivariate stepwise logistic regression analyses

After adjustment with age, sex, duration of education, BMI, clinic for GERD, RDQ score, TDQ score, and metabolic syndrome, multivariate logistic regression analysis showed that the combined group had a higher RDQ score than the daytime or nighttime group ($p < 0.0001$). Furthermore, the

Table 3 Comparison of clinical factors in patients with either nighttime or combined symptoms with daytime symptoms using multivariate stepwise logistic regression analyses.[a]

	Nighttime			Combined		
Variable factors	OR	95% CI	p	OR	95% CI	p
Female gender	0.747	0.401–1.392	0.36	0.855	0.58–1.259	0.43
Age	1.001	0.97–1.032	0.97	0.994	0.973–1.016	0.59
Duration of education (Ref.[b] < 9 y)						
9–12 y	0.948	0.386–2.326	0.22	1.846	1.067–3.194	0.27
>12 y	2.136	0.909–5.018	0.02	2.15	1.23–3.759	0.03
BMI	1.133	1.033–1.244	0.01	1.091	1.022–1.164	0.01
Clinic for GERD	0.773	0.425–1.405	0.40	1.374	0.932–2.023	0.11
RDQ score	0.99	0.933–1.051	0.75	1.093	1.054–1.133	<0.0001
TDQ score	1.021	0.979–1.066	0.32	1.025	0.999–1.051	0.06
Metabolic syndrome	0.923	0.447–1.905	0.83	1.169	0.717–1.906	0.53

BMI = body mass index; CI = confidence interval; GERD = gastroesophageal reflux disease; MS = metabolic syndrome; OR = odds ratio; PSQI = Pittsburg Sleep Quality Index; RDQ = reflux disease questionnaire; Ref. = reference; TDQ = Taiwanese Depression Questionnaire.
[a] OR and 95% CI were obtained from multivariate logistic regression adjusted for gender, age, education, BMI, clinic for GERD, RDQ score, PSQI score, and MS.
[b] Ref. means that category served as the reference group for calculating an OR.

combined or nighttime group had a higher BMI and a longer duration (> 12 years) of education than the daytime group (Table 3).

Discussion

In this study of 651 symptomatic GERD patients from a health examination center, 224 (34.4%) had erosive esophagitis on endoscopy and 467 (71.7%) suffered from nighttime reflux. In *post hoc* analysis, patients with combined daytime and nighttime reflux had a higher RDQ score than those with daytime reflux only, suggesting that the severity of reflux symptoms was higher in patients having reflux symptoms during both daytime and nighttime. In addition, higher BMI and education level were factors associated with nighttime reflux.

Nighttime reflux symptoms are common in GERD patients.[22,23] A large sample study revealed that 72% of GERD patients had typical nighttime reflux symptoms. Among 1000 adults experiencing heartburn at least once per week, assessed using a nationwide telephone survey, 79% had heartburn at night. In our study, 60.8% of GERD patients had combined daytime and nighttime reflux, and 10.9% had isolated nighttime reflux, which was comparable with the findings of previous studies. Our study divided nocturnal GERD patients into two groups, combined daytime and nighttime reflux group and isolated nighttime reflux group, which helped in better understanding of the nighttime reflux.

Nocturnal GERD can produce more severe consequences than daytime GERD, especially in the quality of sleep and productivity of daytime work.[24] Furthermore, patients with nighttime reflux symptoms had a higher score of "GERD symptom and medication questionnaire" than those with exclusively daytime symptoms.[25] Using 24-hour esophageal PH monitoring, the number of reflux events lasting > 5 minutes and acid contact time were significantly greater in patients with nighttime heartburn than in those without it for the total and upright position time.[26] In our study, those with combined daytime and nighttime reflux had more severe reflux symptoms than those with daytime reflux, but there was no difference compared with those with isolated nighttime reflux. Taking these results together, nighttime reflux is more troublesome than daytime reflux.

In a study of 50 GERD patients who received intraesophageal PH monitoring during nighttime, it was found that the number of acid reflux, time of PH < 4, and frequency of PH < 4 during nighttime were significantly lower in nonerosive reflux disease (NERD) patients compared with patients with erosive esophagitis.[27] It suggested that the severity of intraesophageal acid exposure during nighttime might cause the difference between NERD and erosive esophagitis patients. By contrast, our results showed no difference in the presence of erosive esophagitis on endoscopy among patients of the daytime, nighttime, or combined group. The inconsistent finding can be explained due to dissociation between the severity of reflux symptom and the intensity of intraesophageal PH.

Obesity is a well-known risk factor of GERD.[28] However, studies investigating the association of nighttime reflux with obesity are scarce. In a large prospective cohort study, increased BMI was found to be associated with heartburn during sleep.[9] Our results showed that the nighttime or combined group of GERD patients had higher BMI than the daytime group. It suggests that obesity may play an important role in the development of nighttime reflux.

It is an interesting finding about the association between duration of education and the timing of reflux symptoms in our study. Patients either with combined daytime and nighttime reflux or with isolated nighttime reflux have a higher frequency of longer duration (> 12 years) of education than those with daytime reflux. As we know, people get knowledge from education and knowledge can affect their behavior including dietary habit, exercise, and lifestyle.[29,30] However, a better understanding of the complex interplay between education, behavior, and disease pattern needs additional studies.

Whether nighttime reflux can affect the quality of sleep is an important issue. In a study using a telephone survey, 75% of nocturnal GERD patients reported impaired sleep quality.[7] Using the PSQI questionnaire, patients with nighttime heartburn had significantly impaired subjective sleep quality compared to those without it.[24] Two previous studies have shown that esomeprazole improved both heartburn symptoms and sleep quality compared with placebo in patients having both moderate-to-severe nighttime heartburn and sleep disturbance, providing further evidence on the adverse impact of nighttime heartburn on sleep quality.[31,32] However, our results failed to demonstrate the difference of sleep quality among patients with daytime, nighttime, or combined reflux. The possible explanation is relatively mild reflux symptoms in this study population from a health examination center.

This study has several strengths. In literature, symptomatic GERD is usually divided into two types according to the time of reflux symptoms: one is daytime GERD and the other is nocturnal GERD, which is defined as the presence of nighttime reflux regardless of whether daytime reflux is present or not. This study population was categorized into three groups including patients with daytime, nighttime, or combined reflux symptoms. This classification can precisely elucidate the clinical characteristics and psychosocial impact of each group. In addition, this is the first study to investigate the impact of different timings of reflux symptoms on anxiety and depression using TDQ and STAI scores. However, some limitations of our study should be acknowledged. First, a late night snack may affect the risk of nighttime reflux.[33] However, these data were not collected from each participant in this study. Second, some drugs are known to increase the risk of reflux symptoms and esophageal mucosal injury.[34] In this study, although the history of medication of each participant was not recorded, this confounding effect might be minimal due to fewer drug users in this relatively healthy population. Finally, since this study was cross-sectional, the causal relationship could not be determined.

In summary, although GERD patients with combined reflux symptoms have more troublesome symptoms than those with daytime reflux, the timing of reflux symptoms has no influence on the development of erosive esophagitis, quality of sleep, anxiety, and depression. In addition, GERD patients with nocturnal or combined reflux symptoms have higher BMI and education level than those with daytime reflux. Our study confirms the hypothesis that GERD patients with different timings of reflux symptoms have different clinical

characteristics in terms of BMI and duration of education, but not in terms of the presence of esophagitis on endoscopy, quality of sleep, and psychosocial status.

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